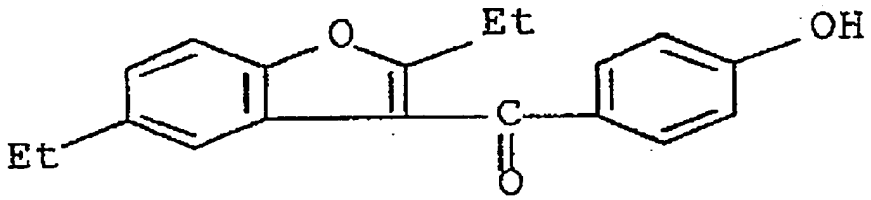
REMARKS

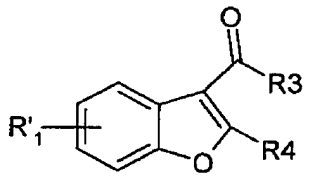
The Office Action mailed March 5, 2008 has been carefully considered together with each of the references cited therein. The amendments and remarks presented herein are believed to be fully responsive to the Office Action. Reconsideration of the present Application in view of the following remarks is respectfully requested.

Applicant has amended the Application to attend to housekeeping matters and to more clearly describe the invention. Applicant amended the title of the invention to attend to housekeeping matters to make the title consistent with the claims. Applicant has amended the claims of the Application to more clearly recite what Applicant believes to be the invention. In claim 1, Applicant more clearly recites that the process of preparing compounds of formula (I) consists of reacting the 2-alkyl-3carboxybenzofuran of formula (II) with a halogenating agent to produce the compound of formula (III) which is further reacted with an alkyl phenyl ether in the presence of a Lewis acid to provide a mixture of formula (IV) and (IVa), and following dealkylation, optionally isolating the product of formula (I). It is not believed that any new matter was introduced by these amendments, and that no additional search is required by the office.

Claim 16 was rejected under 35 U.S.C. 102(b) as being anticipated by Bisagni et al. (Bulletin de la Societe Chimique de France (1960), pages 1968-1976). The rejection of claim 16, under 35 U.S.C. 102(b) as being anticipated by Bisagni et al. (Bulletin de la Societe Chimique de France (1960), pages 1968-1976) should be withdrawn for the reason that Bisagni et al. does not contain all the elements of Applicant's invention. Bisagni et al discloses benzofurans according to the following formula:



wherein with reference to the formula in claim 16 (repeated hereinbelow)

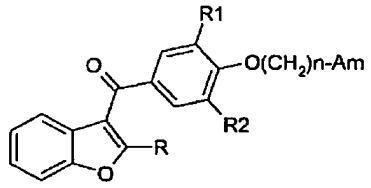


(V)

R_1' is an ethyl group, but Bisagni et al. differs from the instant invention wherein R_1' is a nitro group. Applicant respectfully points out the as written, claim 16, does not permit R_1' to be an ethyl group. Therefore, the rejection of claim 16, as amended under 35 U.S.C. 102(b) as being anticipated by Bisagni et al. (Bulletin de la Societe Chimique de France (1960), pages 1968-1976) should be withdrawn for the reason that the process of Bisagni et al. (Bulletin de la Societe Chimique de France (1960), pages 1968-1976) requires a side branch on an aromatic ring which is not part of applicant's claimed invention. It is fundamental that all elements of a claim must be found united in the same way to perform the identical function for a reference to establish anticipation. Anticipation is a technical defense which must meet standards: Unless all of the same elements are found in exactly the same situation and united in the same way to perform the identical function in a single prior art reference, there is no anticipation. Unless all of the elements of an claimed invention can be found in a single reference, it cannot be said that such a claim is anticipated by that reference.

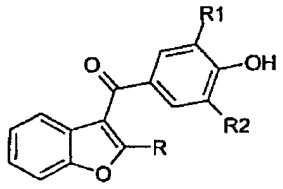
Claims 1-15, and 21 were rejected under 35 U.S.C. §103(a) as being unpatentable over Descamps et al. (DE 2347196, which is assumed to be equivalent to US Patent No. 3,920,707 and for the purposes of this response will be referred to as the '707 Patent). The rejection of claim 1 as amended under 35 U.S.C. §103(a) as being unpatentable over being unpatentable over Descamps et al. (DE 2347196, the '707 Patent) should be withdrawn for the reason that while analogy is at times useful, organic as well as inorganic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected, and for the reason that the '707 Patent teaches away from Applicant's invention as recited in amended claim 1, and for the reason that no one skilled in the art, based solely on the

disclosure of the '707 Patent, which is based on a starting material having an unsubstituted aromatic ring, would find any guidance or expectation of success in producing the para-species selective process of the instant invention, when the Descamps disclosure is silent on producing either the para or the ortho species intermediate product which when dealkylated provides the compound of Applicant's formula (I). Applicant's invention as recited in claim 1 relates to the discovery of a process which results in the production of an intermediate mixture of 2-alkyl-3-(4-alkoxybenzoyl)benzfuran (para species) and 2-alkyl-3-(2-alkoxybenzoyl)benzfuran (ortho species), wherein the para species is predominantly present at high purity and on subsequent dealkylation provides the 2-(n-alkyl)3-(4(hydroxybenzoyl)benzofuran at high purity and high yield, without requiring an additional separation step. The German reference, DE 2 347 196 , Descamps et al and the '707 Patent relate to benzofuran derivatives and to pharmaceutical compositions containing these benzofuran derivatives for clinical use in treatment of angina pectoris. Also disclosed is a method for preparing the benzofuran derivatives. It is important to note that the '707 Patent discloses the compound and a method for preparing describe a process for the manufacture of compounds of formula **1** wherein the aromatic ring does not have any substituents:



1

The '707 Patent requires that R1 and R2 must be identical and that R1 and R2 are both either hydrogen or both identical straight chain alkyl groups containing from 1 to 3 hydrocarbons (See '707 in column 1, lines 25-28. The disclosure provides separate and distinct methods for preparing the compounds or the above formula 1, depending on whether the R1 and R2 are both hydrogen (Route I) or are both straight chain alkyl groups(Route II). The compounds of the above formula 1 ('707 Patent) are prepared from compounds of formula **2** :

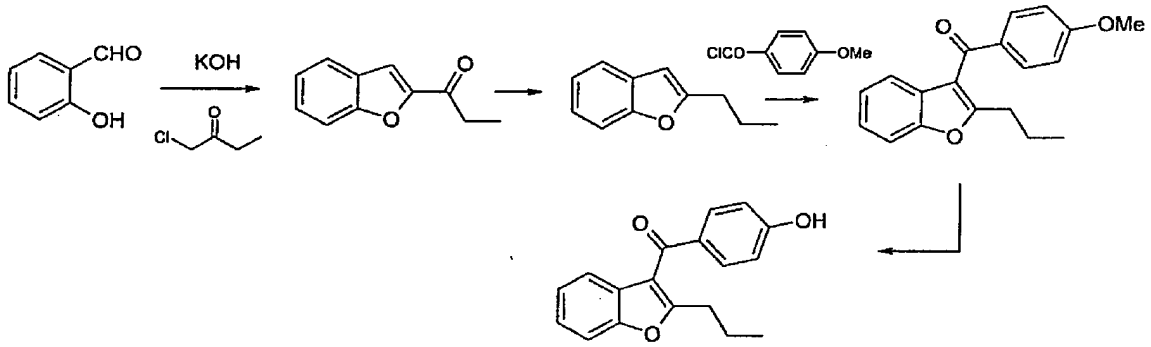


2

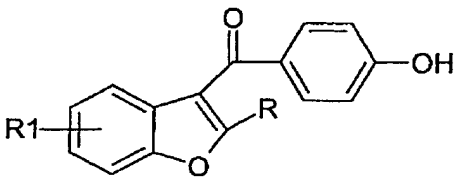
And according to the disclosure of Descamps, the compounds of formula 2 are prepared in 2 different ways (See DE 2 437 196 , pages 5,6 or '707 Patent at column 2, line 48 to column 3, line 33) and are reproduced hereinbelow as I. and II.

I. **When R1 = R2 = H:**

The compounds of formula 2 are prepared according to British Patent Specification GB 836272 from salicylaldehyde; as shown below as the following scheme 1:



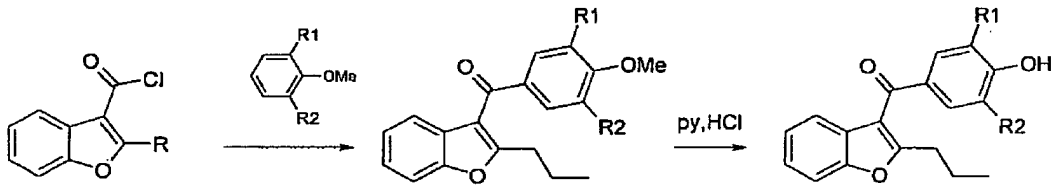
The above process of scheme I, wherein R1 = R2 = H is completely different from the process of the instant invention as recited in claim 1 where R1=R2=H and results in a different product, because in the '707 patent of Descamps, the aromatic ring is not substituted. Applicant's claim 1 requires a substituted aromatic ring with an R1 subtitutient as shown below:



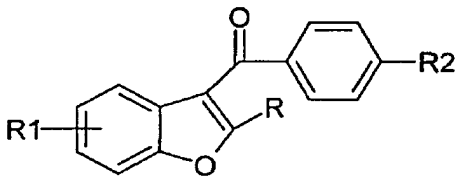
(I)

II. **When R1 = R2 are identical alkyl groups and not hydrogen atoms:**

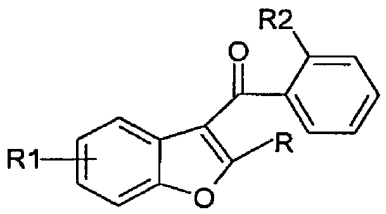
The compounds of Decamps formula 2 are prepared as shown below as the following scheme II where R1 and R2 are identical and contain from 1 to 3 carbon atoms:



As in scheme I above, the aromatic ring in the final product of scheme II is not substituted, contrary to Applicant's general formula as recited in claim 1 of the instant invention. In addition, this product differs from Applicant's process by the presence of the R1 and R2 groups. Scheme II of Descamps discloses a Friedel Crafts reaction from **2,6-disubstituted** anisole and a benzofurancarboxylic chloride. Because the aromatic ring is unsubstituted, the process of Descamps is silent on any **problem related to para/ortho selectivity in the reaction, because the ortho by product can not be formed. Thus, no one skilled in the art would be motivated to select only those elements of the sepatare reaction sequences disclosed in the '707 Patent to arrive at Applicant's process without the improper use of hindsight.** Furthermore, Applicant unexpectedly discovered that when R1 and R2 are the same and are both H, that in Applicant's process, in the intermediate mixture, the para species is formed in an extremely high selectivity : (See page 6 of Applicant's Specification) :



(IV)
PARA SPECIES



(IVa)
ORTHO SPECIES

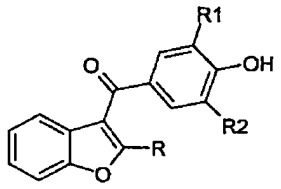
" ... The readily result, by a Friedel-Crafts reaction, essentially in a 4-alkoxy derivative and very little 2-alkoxy derivative , generally in a ratio of 95/5 to 97/3 . "

This unexpected result makes it possible to carry out the subsequent dealkylation step on the mixture of the 4-alkoxy derivative (para) and of the 2-alkoxy derivative (ortho) without having to perform any preliminary separation of the two species in order to obtain the desired product with an unexpectedly high yield and high purity. Thus the synthesis of compounds of general formula **2** by a Friedel-Crafts reaction according to scheme 2 **when R1=R2=H** is not obvious over or disclosed in the '7-7 Patent or in the German Language equivalent (DE2437196). In the '707 Patent of Descamps et al., all the examples are given with R1,R2 = alkyl groups. Descamps doesn't teach a process with a Friedel- Crafts reaction with alkyl phenyl ether such as anisole with unsubstituted 2,6 positions as disclosed in the instant invention, and when the R1 and R2 groups are both hydrogen, the '707 Patent disclosure teaches away from the instant invention by disclosing the use of the procedure according to the British disclosure GB836272 which is a completely different process and also does not disclose any substiuent on the aromatic ring. Furthermore, no one skilled in the art would have been able to predict applicant's discovery that Applicant's process favors the production of the par species as an intermediate product which results in the production of the product of Applicant's formula 1 at high yield and high selectivity which can eliminate purification steps. Applicant's invention makes it possible to prepare the intermediate product advantageously without a difficult preliminary separation of isomers and with a purity such as to permit the direct use of the raw reaction product in the subsequent stages, thus avoiding tedious purification process. The invention as a whole must be considered in deciding

the question of obviousness. Therefore, the rejection of claim 1, as amended, should be withdrawn for the reason that under 35 U.S.C. §103(a) as being unpatentable over being unpatentable over Descamps et al. (DE 2347196, the '707 Patent) should be withdrawn for the reason that while analogy is at times useful, organic as well as inorganic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected, and for the reason that the '707 Patent teaches away from Applicant's invention as recited in amended claim 1, and for the reason that no one skilled in the art, based solely on the disclosure of the '707 Patent, which is based on a starting material having an unsubstituted aromatic ring, would find any guidance or expectation of success in producing the para-species selective process of the instant invention, when the Descamps disclosure is silent on producing either the para or the ortho species intermediate product which when dealkylated provides the compound of Applicant's formula (I).

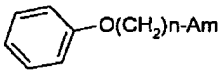
The rejection of claims 2-15, and 21 under 35 U.S.C. §103(a) as being unpatentable over Descamps et al. (DE 2347196, which is assumed to be equivalent to US Patent No. 3,920,707) should be withdrawn for the reasons given in support of claim 1 as amended from which they depend.

Claims 1-15 and 21 were rejected under 35 U.S.C. §103(a) as being unpatentable over Gubin et. al. European Journal of Medicinal Chemistry (1974), 9(1), pages 19-25(hereinafter referred to as the Gubin reference). The rejection of claim 1 under 35 U.S.C. §103(a) as being unpatentable over Gubin et. al. European Journal of Medicinal Chemistry (1974), 9(1), pages 19-25, should be withdrawn for the reason that the reference teaches away from Applicant's invention. Applicant notes that the Gubin reference names many of the same inventors named in the above mentioned '707 Patent and the German Patent DE 2347196 and as discussed hereinabove relates to methods of producing compounds of the formula 2 of the '707Patent wherein the substituents R1 and R2 are the same and are alkyl groups having 1 to 3 carbon atoms:



2

Clearly, there is no disclosure in the Gubin reference of any compounds wherein R1 and R2 are hydrogen and no compounds wherein the aromatic ring has any substituent. The only disclosure in the Gubin reference is the same as the disclosure of the '707 Patent which teaches away from the Fridel-Crafts acylation with alkylphenyl ether in favour of the disclosure of the British Patent GB 836272. In table I and II of the publication, R2 are alkyl groups and not hydrogen atoms. The Friedel-Crafts reaction thus mentioned are described from dialkyl anisoles and not with anisole. In table III of the Gubin publication , R2 = H but the products are obtained according to Fig 2 of the publication and not from a Friedel-Crafts reaction from the benzofuranecarboxylic acid chloride and the corresponding phenoxy derivative :

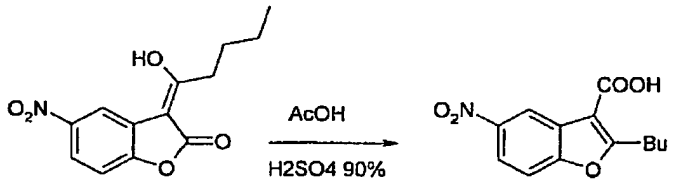


showing that compounds are obtained in a different way than the instant invention as recited in amended claim 1. Therefore, the rejection of claim 1 as amended under 35 U.S.C. §103(a) as being unpatentable over Gubin et. al. European Journal of Medicinal Chemistry (1974), 9(1), pages 19-25, should be withdrawn for the reason that the reference teaches away from Applicant's invention and for the reasons given hereinabove with reference to the US Patent 3,920,707 which discloses the same compounds and processes. The rejection of claims 2-15 and 21 under 35 U.S.C. §103(a) as being unpatentable over Gubin et. al. European Journal of Medicinal Chemistry (1974), 9(1), pages 19-25, should be withdrawn for the reasons given in support of claim 1, as amended from which claims 2-15 and 21 depend.

Regarding the Examiner's assumption that the reactions disclosed in the '707 Patent are independent of the substituents, Applicant respectfully points out that the reaction functionalities are apparently affected by substitutions as evidenced by the different routes to the product based on the nature of R1 and R2 of formula 2 in the '707 Patent as discussed hereinabove.

Claims 18-20 were rejected under 35 U.S.C. §103(a) as being unpatentable over Chatterjea (Journal of Indian Chemical Society, 1957, Vol. 34(4), pages 299-305. The rejection of claim 18 under 35 U.S.C. §103(a) as being unpatentable over Chatterjea (Journal of Indian Chemical Society, 1957, Vol. 34(4), pages 299-305, should be withdrawn for the reason that no one skilled in the art would have any expectation of success in view of Applicant's surprising discovery that the required transformation requires that the acid catalyst must be present in a concentrated aqueous solution of at least 80 percent by weight. As recited in claim 18, Applicant's process relates to the preparation of 2-(n-butyl)-3-carboxy-5-nitrobenzofuran. In Applicant's Specification, on page 8, Applicant discloses that the compound (VI) "...is treated by heating, preferably in a carboxylic acid , in particular acetic acid , and **by an acid catalyst in a concentrated aqueous solution at least 80% by weight**..." to form the desired compound (II) which can be isolated. This is exemplified in the example 1 of Applicant' Specification and reproduced hereinbelow:

Example 1 : preparation of 2-(n-butyl)-3-carboxy-5-nitrobenzofuran

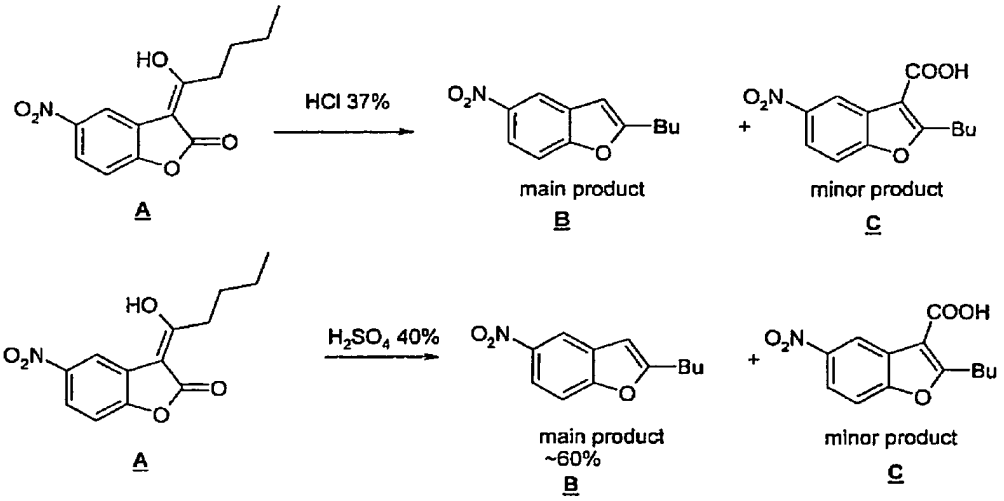


main product
76% yield

In the publication of Chatterjea , such reaction is performed with different starting materials and other substituents in the presence of concentrated HCl , the concentration of which is **37%** maximum. In a Declaration filed under 37

C.F.R 1.132 by Alain Shouteen, Applicant presents additional examples which clearly show the unexpected benefits of the instant invention in a side-by-side comparison with the process disclosed in the Chatterjea Publication. In the publication of Chatterjea, (Chatterjea (Journal of Indian Chemical Society, 1957, Vol. 34(4), pages 299-305) such reaction is accomplished with different starting materials and other substituants with concentrated HCl, the concentration of which is **37%** maximum. Although Chatterjea does not specifically indicate the concentration of the HCl used, Chatterjea does disclose a concentrated HCl solution which means **37%** in water (See Experimental, p 301 , second example : 2-o-Methoxybenzylcoumarone-3-carboxylic Acid). The concentration of 37 weight percent HCl is the concentration of the commercial concentrated aqueous HCl. Higher HCl concentration could be obtained, but this requires solutions under pressure which is not the case here. In the other examples of Chatteerjea, at page 303, 2-Methylcoumarone-3-carboxylic Acid , example (b), Chatterjea mentions **HCl (4cc)**, and latter in the example at page 305 " Isomerisation of the Self-condensation Product" **HCl (1,5 cc)** is also interpreted to mean HCl conc, i.e., 37% according to the previous examples.

Applicant discovered that when concentrated HCl is used for the synthesis of (II) from (VI) or (VII), the main product is not the expected product (II) but the product of decarboxylation as well as when diluted sulphuric acid is used.



In order to compare the experiments disclosed in the Chatterjea Publication, the following experiments were carried out to show the influence of the concentration of the acid employed in the reaction:

Influence of the acid catalyst by using operating conditions of Chatterjea

The following experiments were run using the conditions very similar to the conditions disclosed in Chattejea and are shown in Table A:

Table A

	Starting material A	Acetic acid	Strong acid	operating conditions	Crude yield B	Crude yield C
example 1	0,876g	25g	25g HCl conc. 37%	102°C ; 7hours	59%	9%
example 2	0,876g	25g	28g H2SO4 44%	100°C ; 3,25 hours	51%	3%
example 3	8,68g	61,41g	16,4g H2SO4 40%	116°C ; 7 hours	58%	4%

Note: **B** and **C** refer to the species shown in the above figure showing the species produced.

Experimental procedures which were followed for Experiment 1-3 in Table A are summarized hereinbelow.

Example 1:

0,876g of **A** (3.33 mmoles) were mixed with 25g of acetic acid and 25g of concentrated HCl solution 37%. The resulting mixture was then heated at 102°C during 7 hours. A sample was taken and analyzed by HPLC (High Pressure Liquid Chromatography) for determining the crude yields for species **B** and **C**.

Example 2:

0,876g of **A** (3.33 mmoles) were mixed with 25g of acetic acid and with 28,15g of a 44% aqueous sulfuric solution (i.e., containing 12,4g of concentrated sulfuric acid and 15,75g of water). The resulting mixture was then heated at 100°C during 3,25 hours. A sample was taken and analyzed by HPLC for determining the crude yields for **B** and **C**.

Example 3 :

8,68g of **A** (0,033 moles) were mixed with 61,41g of acetic acid and with 16,175g of a 40% aqueous sulfuric solution (ie containing 6,47g of concentrated sulfuric acid and 9,705g of water). The resulting mixture was then heated at 116°C during 7 hours. A sample was taken and analyzed by HPLC for determining the crude yields for **B** and **C**

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Filed : 11/29/2006
Response to Office Action Mailed 03/05/2008

These procedures and conditions can be seen to be very similar to those disclosed in the Chatterjea Publication which are summarized hereinbelow in Table B:

Table B

		starting material	Acetic acid	HCl	final products
Chatterjea	example p 301	0,6g	3cc = 3,1g	1cc=1,19g HCl conc	no yield given
Chatterjea	example p 303	0,5g	6cc = 6,3g	4cc = 4,76g	no yield given

Thus, the results in Table A clearly show that by using HCl conc. 37% as Chatterjea disclosed, that the species **B** is mainly formed, and that the species **C** is the minor product . Thus, HCl conc 37% as well as diluted H_2SO_4 are not suitable reactants for synthesizing a major portion of the species product **C**.

In order to further emphasize the influence of the acid concentration on the selectivity and yield of the species, a series of further experiments were performed. The effect of the acid concentration on the yield of product species B and product C are shown in Table C, wherein the acid concentration in increased from a level of 20 to 85 weight percent. The procedure for each of the experiments 4-10 is illustrated by the following description of the procedure for Experiment 6:

Example 6 : 9,53g of **A** (36,2 mmoles) were mixed with 34,75g of acetic acid , and with 11,82g of a 60% aqueous sulfuric acid solution (i.e., containing 7.24g of concentrated sulfuric acid 98% and 4.58g of water). The resulting mixture was then heated at 118°C during 7 hours. A sample was taken and analyzed by HPLC for determining the crude yields for product species **B** and product species **C**.

Influence of the concentration of the acid catalyst :

The following Table C shows the influence of the concentration of the strong acid H_2SO_4 :

Table C

	H2SO4 Concentration (a)	operating conditions	Crude yield	
			B	C
example 4	85	126°C ; 3,5 hours	14%	65%
example 5	75	118°C ; 6 hours	27%	47%
example 6	60	118°C ; 7 hours	48%	30%
example 7	50	116°C ; 7 hours	59%	12%
example 8	40	116°C ; 8 hours	65%	3%
example 9	30	111°C ; 10 hours	45%	1%
example 10	20	110°C ; 12 hours	34%	0

(a) : concentration of the initial H2SO4 in water

One can clearly see that when increasing the concentration of sulfuric acid, the yields increase for Applicant's desired product species **C**. Applicant discovered that when the acid concentration is increased above 80 weight percent that the production species C is produced as a major product compared to the acid levels of the Chatterjea Publication where species C is only produced in a minor amount. This was exemplified a 90% Sulfuric acid in the example of Applicant's Specification (See "preparation of 2-(n-butyl)-3-carboxy-5-nitrobenzofuran"), an isolated yield of 76% is obtained for species **C** ("...202.5g of a beige product are obtained ... " starting from 263g of 3-(1-hydroxypentylidene)-5-nitro-3H-benzofuran-2-one **A**).

Clearly, Applicant's discovery is unobvious in view of the Chatterjea publication for the reason that Chatterjea discloses significantly lower acid concentrations, and for the reason that Applicant unexpectedly discovered that such lower acid concentrations were insufficient to obtain the selectivity to Applicant's desired product. In addition Applicant discovered that it was critical to maintain the acid concentration above 80 percent by weight in the concentrated aqueous solution in order to obtain selectivity in Applicants process. The concentration of the aqueous solution of the acid is very important to get the desired product (II) in good isolated yields from product of general formula (VI) or (VII). Therefore, the rejection of claim 18 under 35 U.S.C. §103(a) as being unpatentable over Chatterjea (Journal of Indian Chemical Society, 1957, Vol. 34(4), pages 299-305, should be withdrawn for the reason that no one skilled in the art would have any expectation of success in view of Applicant's surprising discovery that the required transformation requires that the acid catalyst must be present in a concentrated aqueous solution of at least 80 percent by weight. The rejection

of claim 19 under 35 U.S.C. §103(a) as being unpatentable over Chatterjea (Journal of Indian Chemical Society, 1957, Vol. 34(4), pages 299-305, should be withdrawn for the reasons given in support of claim 18 from which claim 19 depends.

It is respectfully submitted that, in view of the above remarks the rejections under 35 U.S.C. 102 and 103, should be withdrawn and that this application is in a condition for an allowance of all pending claims. Accordingly, favorable reconsideration and an allowance of all pending claims are courteously solicited.

An early and favorable action is courteously solicited.

Respectfully submitted,

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Attachment:
Declaration under 37 C.F.R. 1.132